Effect of Orlistat on Weight Regain and Cardiovascular Risk Factors Following a Very-Low-Energy Diet in Abdominally Obese Patients

A 3-year randomized, placebo-controlled study

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OBJECTIVE — To investigate the efficacy of orlistat on the maintenance of weight loss over 3 years following a major weight loss induced by very-low-energy diet (VLED) in obese patients with metabolic risk factors such as dyslipidemia, impaired fasting glucose, and diet-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS — Initially, weight loss was induced by an 8-week VLED (600–800 kcal/day) in 383 patients with a mean BMI of 37.5 kg/m^2 (range 30.0–45.2). Those who lost ≥5% of their body weight (309 of 383 patients) were then randomized to receive lifestyle counseling for 3 years together with either orlistat 120 mg t.i.d. or matching placebo capsules. Primary end points were the maintenance of ≥5% weight loss after 3 years. Additionally, differences in the development of type 2 diabetes between orlistat and placebo were analyzed.

RESULTS — The VLED induced a mean weight loss of 14.4 ± 2..0 kg among the subsequently randomized patients. The mean weight gain after 3 years was lower with orlistat than with placebo (4.6 ± 8.6 vs. 7.0 ± 7.1 kg; $P < 0.02$). The number of participants who achieved ≥5% weight loss also favored orlistat (67 vs. 56%; $P = 0.037$). Waist circumference was significantly more reduced in the orlistat group ($P < 0.05$), but no other differences in the risk factors were observed between the two groups. The incidences of new cases of type 2 diabetes were significantly reduced in the orlistat group (8 cases out of 153 subjects) versus placebo (17 cases out of 156 subjects) ($P = 0.041$).

CONCLUSIONS — The addition of orlistat to lifestyle intervention was associated with maintenance of an extra 2.4 kg weight loss after VLED for up to 3 years in obese subjects. The combination of orlistat and lifestyle intervention was associated with a reduced occurrence of type 2 diabetes.

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Abbreviations: VLED, very-low-energy diet; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The relation between obesity and several of its comorbidities, such as type 2 diabetes and premature atherosclerosis, seems to be mediated by risk factors characterized by the metabolic syndrome (1,2). The metabolic syndrome is closely associated with abdominal obesity (3–6). Weight loss and increased physical activity are the cornerstones in the treatment of the metabolic syndrome. Treatment success defined as clinically meaningful weight loss that can be maintained for longer periods is, however, limited (7–9).

The lipase inhibitor orlistat (Xenical) has been shown to promote additional weight loss compared with lifestyle modifications alone (10,11). Moreover, studies (12,13) have shown improvement in insulin sensitivity and glucose homeostasis with orlistat treatment in both diabetic and nondiabetic obese patients. Recently, the XENDOS (XENical in the Prevention of Diabetes in Obese Subjects) Study has indicated that the additional weight loss induced by orlistat reduced the development of type 2 diabetes by 37% during the 4-year study in obese patients (14).

Very-low-energy diets (VLEDs; 400–800 kcal/day) containing a high amount of protein may induce major short-term weight loss. However, the long-term maintenance of this weight is generally disappointing (15). Accordingly, we examined the effect of orlistat on long-term weight regain after weight loss induced by a VLED in obese subjects with metabolic risk factors. Our research question was whether treatment with orlistat in addition to lifestyle change maintains weight loss after a VLED better compared with lifestyle modifications alone. Thus, in this study major weight loss was induced by VLED and then followed by randomized, double-blind treatment with orlistat or placebo for 3 years. Additionally, we analyzed the changes in the metabolic risk profile and the development of type 2 diabetes during the study.

RESEARCH DESIGN AND METHODS — Eligible subjects were men and women (in ratio 1:1) aged 18–65 years with abdominal obesity defined as a BMI between 30 and 45 kg/m^2 and a waist circumference ≥102 cm (men) or ≥92 cm (women). Furthermore, participants were required to have one or more of the following risk factors: impaired fasting glucose (plasma glucose ≥6.1 mmol/l), diet-treated type 2 diabetes (plasma glucose ≥7.0 mmol/l) or dyslipidemia (HDL cholesterol ≤0.9 mmol/l [men] or ≤1.1 [women]), and/or serum triglycerides ≥2.0 mmol/l but <10.0 mmol/l.

The patients were recruited at nine clinical research centers in Scandinavia. All provided written, informed consent. The study was conducted according to the Helsinki Declaration and was approved by the ethical committees in each of the four countries. After screening, 383 participants were prescribed a VLED (Modifast; Novartis, Basel, Switzerland or Nutrilett; Nycomed Pharma, Oslo, Norway) of 600–800 kcal/day for 8 weeks. During the 8 weeks, the patients were followed weekly by registered dietitians. A body weight loss of ≥5% during the VLED period was a prerequisite for randomization into the 3-year weight maintenance period. The number of participants obtaining at least 5% weight loss after the VLED was 309, or 80.7%, of the total that started in the study. These subjects were randomly assigned to 3 years of treatment with either orlistat capsules (120 mg t.i.d.) or matching placebo capsules. At randomization, the population was stratified according to sex, center, and the degree of weight loss after VLED. The patients were randomly assigned in equal numbers to each group using a minimization algorithm. A central randomization was used.

After the VLED, the participants were instructed to follow a standard energy-restricted diet (600 kcal daily deficit) during the following 3 years of the intervention. Patients were monitored every month for the first 18 months and then at 3-month intervals. A dietitian provided dietary and lifestyle counseling at each visit, and the dietitians were instructed to give the same advice at all centers. Patients were advised to reduce fat to ~30% of total energy, in particular saturated fat by limiting dairy fats and oils and substituting poultry, fish, and lean meats for fatty meats and increasing the intake of fruits and vegetables and limiting sweets, cookies, and desserts. Advice to increase daily physical activity was also given. The patients completed weighed dietary records by describing and weighing all food and beverages that were consumed for 3 consecutive days 1 month and 1 year after the VLED. The study medication returned by the patients at clinic visits was counted.

If glucose control deteriorated in patients with type 2 diabetes, metformin was started according to a predetermined plan. If the A1C level exceeded 10% after maximal metformin treatment (2 g daily), the subject should be withdrawn from the study. Medication for high blood pressure was allowed. At inclusion, lipid-lowering drugs were not allowed but treatment with statins for hyperlipidemia was allowed, if deemed necessary according to the judgment of the investigator. Almost two-thirds of the randomized participants (200 of 309) completed the 3-year study.

The body weight (with a calibrated scale at each center and with the patients in underwear without shoes), waist circumference (measured midway between lower costa and crista), and blood pressure were determined. Adverse events and changes of medication were recorded at every visit. Fasting plasma glucose; insulin; C-peptide; A1C; total, HDL, and LDL cholesterol; and triglycerides were measured at a certified central laboratory (Medi-Lab, Copenhagen, Denmark).

Outcome measures

The primary objective was to demonstrate the effect of orlistat on the prevention of body weight regain after an initial weight loss induced by VLED. This was obtained by determining the change in body weight after 36 months of treatment and counting the number of patients who were able to obtain a weight loss of >5% after 36 months. Secondary efficacy variables included changes in waist circumference and metabolic profile. We also analyzed the development of new cases of type 2 diabetes during the study. The development of diabetes was based on changes in fasting glucose from normal or from impaired fasting glucose levels to fasting glucose levels >7.0 mmol/l at two consecutive determinations. The definition also included subjects without a medical history of diabetes who started antidiabetes drug treatment during the study.

Statistical analysis

The data were primarily analyzed in the intention-to-treat population, consisting of all randomized patients who received at least one dose of study drug and had at least one follow-up assessment using the last-observation-carried-forward approach. The analysis of all longitudinal data (such as weight, vital signs, efficacy, etc.) was performed using ANCOVA, with the screening/baseline values as the covariate. The 95% CIs for treatment differences were estimated using LSMeans. Interaction effect between treatment and specific subgroups was also defined in the model. The analysis of primary end point, the treatment success rate, was performed with the Cochran-Mantel-Haenszel test, with all the stratification variables included one at the time. The analysis of the new cases of diabetes was performed using the hazard ratio. The 0.05 level of significance was used for all analyses.

RESULTS — A total of 383 obese men and women met the eligibility criteria and started the VLED treatment. Of these, 309 patients (152 men and 157 women) who achieved ≥5% weight loss after 8 weeks of VLED treatment were randomized in the double-blind, placebo-controlled phase of the investigation. Seventy-four patients (19.3%) who were unable to lose 5% of their body weight during the VLED were excluded. The randomized groups were comparable in regard to age and baseline anthropometric measurements (Table 1). Mean body weight at screening was similar in the two groups. The number of participants with risk factors was not different between the two groups (Table 1).

Weight loss

The weight loss after 8 weeks' VLED was 14.3 ± 2.0 kg in those who were randomized to orlistat and 14.5 ± 2.1 kg in those who were randomized to placebo (Fig. 1). The gain in body weight after VLED to month 36 was significantly less in the orlistat group compared with placebo treatment (4.6 ± 8.6 vs. 7.0 ± 7.1 kg; $P < 0.02$). From before VLED (month = −2) to month 36, the mean weight loss was 9.4 kg (8.3%) after orlistat treatment compared with 7.2 kg (6.4%) after placebo ($P < 0.05$). Treatment success rate predefined as losing at least 5% of initial body weight was 85% in the orlistat group and 72% in the placebo group after 1 year ($P < 0.001$) and 67 vs. 56%, respectively, after 3 years ($P < 0.05$). Weight loss after

Table 1—*Patient characteristics at screening*

	Orlistat	Placebo
n	153	156
Women	77 (50.3)	80 (51.3)
Age (years)	47.2 (20–64)	46.7 (19–63)
Weight (kg)	110 (75–162)	112 (78–152)
BMI (kg/m²)	37.4 (30.1–45.2)	37.6 (30.0–45.0)
Waist (cm)	119 (92–168)	119 (92–144)
Impaired fastin glucose	38 (24.8)	45 (28.8)
Diabetes	38 (24.8)	31 (19.9)
Low HDL	69 (45.1)	65 (41.6)
High triglycerides	91 (59.5)	92 (50.9)

Data are *n* (%) or mean (range). There were no significant differences between the two groups. Low HDL cholesterol ≤0.9/1.1 (mmol/l). High triglycerides >2.0 mmol/l.

3 years at the level of ≥10% was obtained in 34% (orlistat) and 29% (placebo) (NS). Waist circumference was significantly reduced in the orlistat group by 7.7 cm compared with 5.4 cm in the placebo group ($P < 0.05$) after 3 years (Table 2). For completers, the weight regain 3 years after VLED was 5.4 kg in the orlistat group and 8.6 kg after placebo ($P < 0.01$), which was similar to the intent-to-treat population. Baseline characteristics for completers and noncompleters were similar (data not shown).

Sex differences. In predetermined analyses according to sex, the absolute weight loss in women during 3 years was significantly higher in the orlistat group compared with placebo (9.7 kg [8.4%] vs. 6.3 kg [5.3%] weight loss; $P < 0.02$), whereas in men the effect of orlistat compared with placebo was less (8.9 kg [8.3%] vs. 8.1 kg [7.5%] weight loss; NS).

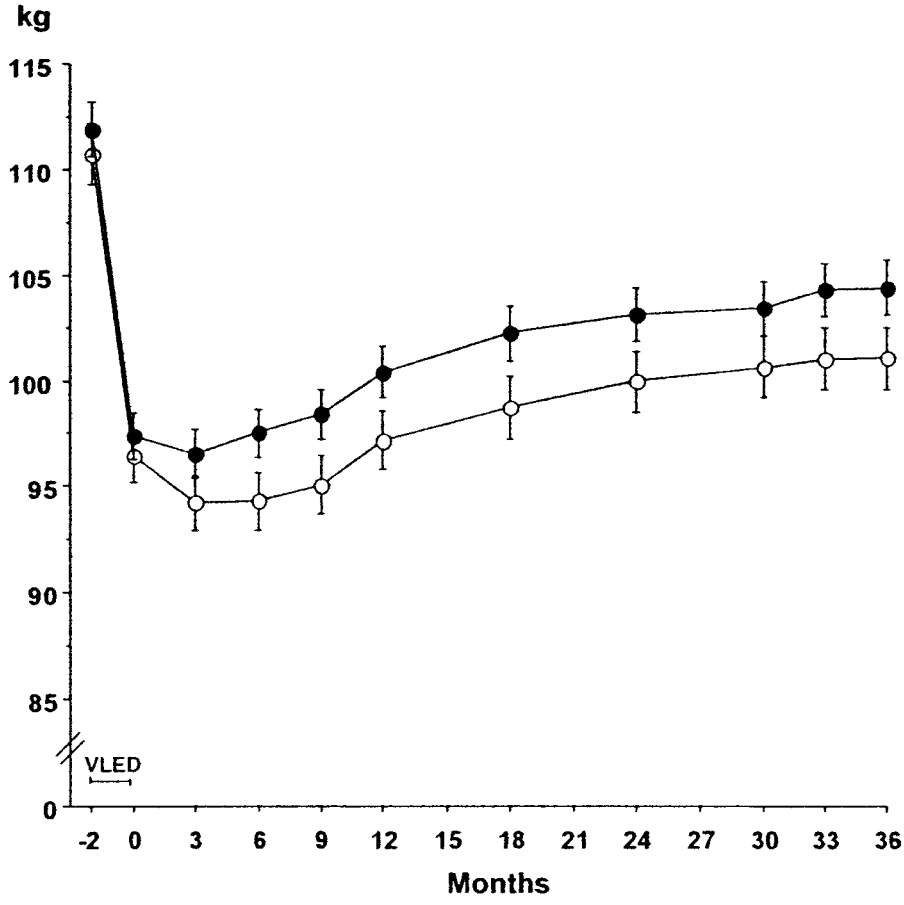

Figure 1.—*Body weight changes during the study. Absolute body weight changes from screening where* t = *0 is at randomization after 8 weeks of VLED. The mean weight loss after VLED in the two groups was 14.4 kg. Means ± SE for the intent-to-treat population. Comparison of weight changes from* t = *0 to 36;* P = *0.0125.* ○*, Xenical;* ●*, placebo.*

Diet

From the dietary records, it was found that the fat content was reduced to a similar degree in the orlistat group (by 19%) and the placebo group (by 22%) (from ~35% of the total energy intake to ~28% in both groups; NS).

Changes in risk factors

As shown in Table 2, all risk factors were significantly ($P < 0.05$) improved after the mean weight loss of 14 kg induced by 8 weeks of VLED treatment. Hereafter, a gradual increment was observed for all the risk factors. With regard to glucose, insulin, C-peptide, and A1C, a tendency to more pronounced reduction in all these parameters was observed after 3 years of orlistat treatment compared with placebo, but these differences did not reach statistical significance for any of the parameters (Table 2).

After VLED, a significant reduction in total cholesterol was observed (20% reduction). Moreover, a pronounced reduction in blood pressure was observed after VLED with a reduction of 12.5 mmHg in systolic blood pressure and a reduction of 7.4 mmHg in diastolic blood pressure. However, after 3 years, there were no differences in total, LDL, or HDL cholesterol and triglycerides between the two treatment groups, but the lipids (except HDL cholesterol) were, however, still significantly lower after 3 years in both groups compared with the initial levels (Table 2).

The number of patients who started with medications with statins, metformin, and medication for high blood pressure during the trial was similar in the two groups. The number of patients treated with metformin was 13 and 18, with statins 11 and 11, and with antihypertensive medication 84 and 90 in the orlistat group and placebo group, respectively. None were withdrawn from the study because of high A1C (>10%).

Changes in the development of type 2 diabetes

New cases of diabetes were recorded, and significantly more patients in the placebo group developed type 2 diabetes (17 subjects [10.9%]) compared with the orlistat

Table 2—*Changes in weight and risk factors during the study*

Time		−2 months	0 months	18 months	36 months	*P* value
Weight (kg)	P	111.9 ± 16.0	−14.3 (−12)	−9.6 (8.4)	−7.2 (−6.3)	0.028
	O	110.7 ± 17.9	−14.5 (−13)	−11.7 (10.4)	−9.4 (−8.3)	
Waist circumference (cm)	P	119 ± 10.9	−12	−9	−5.4	0.032
	O	119 ± 12.1	−12	−12	−7.7	
A1C (%)	P	6.28 ± 0.64	−0.48	−0.34	−0.51	NS
	O	6.32 ± 0.93	−0.54	−0.43	−0.69	
Fasting glucose (mmol/l)	P	6.27 ± 1.54	−0.95	−0.45	−0.32	NS
	O	6.44 ± 1.83	−1.1	−0.67	−0.49	
Fasting insulin (pmol/l)	P	114 ± 58.3	−45	−28	−12	NS
	O	116 ± 65.3	−48	−35	−26	
C-peptid (nmnol/l)	P	1.02 ± 0.39	−0.19	−0.03	+0.16	0.09
	O	1.10 ± 0.43	−0.21	−0.1	+0.05	
Total cholesterol (mmol/l)	P	6.02 ± 1.08	−1.2	−0.13	−0.46	NS
	O	5.91 ± 1.26	−1.2	−0.36	−0.46	
LDL cholesterol (mmol/l)	P	3.77 ± 0.94	−0.80	−0.12	−0.38	NS
	O	3.71 ± 1.04	−0.75	−0.29	−0.34	
HDL cholesterol (mmol/l)	P	1.15 ± 0.26	−0.07	+0.11	+0.06	NS
	O	1.13 ± 0.26	−0.05	+0.06	+0.04	
Triglycerides (mmol/l)	P	2.50 ± 1.41	−0.94	−0.34	−0.43	NS
	O	2.36 ± 1.24	−0.89	−0.32	−0.38	
BT sys (mmHg)	P	144 ± 17.3	−12	−7.2	−8.2	NS
	O	144 ± 19.3	−13	−8.2	−7.8	
BT dia (mmHg)	P	90.7 ± 10.4	−7.6	−4.8	−4.7	NS
	O	90.8 ± 11.6	−7.2	−5.1	−3.7	

Data are *n* (%) or means ± SD. The abdominally obese subjects were randomised after 2 months of VLED (from month −2 to month 0) to receive either orlistat (O) or placebo (P). Values at the various times are absolute changes from initial values (month −2) calculated from the intention-to-treat population. Minus indicates reduction from initial values and plus increment. Body weight changes are also given in percentage (in parentheses). *P* values are given for the absolute changes after 36 months between orlistat and placebo. The time effect at 36 months versus 0 month is significant for all parameters ($P < 0.001$).

treatment (8 subjects [5.2%]) during the 3-year study ($P = 0.041$).

Safety data

Premature withdrawals were similar in the orlistat (33.3%) and the placebo group (37.2%) during the 3-year trial. The withdrawals due to adverse events were 5% in both groups, while the remainder of the withdrawals were due to protocol violation (not enough time, etc.). The only differences in adverse events between the two groups were due to the expected increase in gastrointestinal complications in the orlistat group compared with placebo. These included fatty/oily stool (23 vs. 2.5%), oily spotting (17.5 vs. 0%), abdominal pain (21.5 vs. 16%), and fecal urgency (8.5 vs. 5%) in the orlistat and placebo groups, respectively. In total, 88% in the orlistat group experienced one or more gastrointestinal events (minor, moderate, or severe) during the study compared with 63% in the placebo group ($P < 0.01$). There were 18 subjects in the orlistat group and 28 subjects in the placebo group that experienced a serious adverse event (NS).

CONCLUSIONS— In the present study, we found that the lipase inhibitor orlistat was superior to placebo in maintaining an initial weight loss induced by a VLED for 3 years in subjects who were at high risk of cardiovascular diseases due to abdominal obesity and impaired fasting glucose/diabetes or dyslipidemia. This extra weight loss maintenance obtained with orlistat was associated with reduced development of type 2 diabetes. The VLED effectively induced a major weight loss of ~14 kg after 8 weeks, and this weight loss was associated with pronounced improvements in all metabolic risk factors.

The absolute difference in body weight between the orlistat and placebo groups was ~2.2 kg (i.e., a total of a 9.4-kg weight loss in the orlistat group versus a 7.2-kg weight loss in the placebo group after 3 years' follow-up). Treatment success, as defined as losing at least 5% of initial body weight, was achieved by 67% in the orlistat group compared with 56% in the placebo group after 3 years. The waist circumference was reduced 2–3 cm more in the orlistat group compared with placebo after 3 years ($P < 0.05$). This degree of weight loss after prolonged follow-up has only rarely been observed in the field of obesity, and we believe that the present findings underscore the importance of an initial large weight loss followed by intensive, frequent, and prolonged behavioral therapy.

Only very few long-term (>2 years) intervention studies have been performed with regard to the pharmacological treatment of obesity. Recently, the 4-year study of the effect of Xenical on weight loss and development of diabetes was published (14). This extra weight loss obtained with orlistat in this trial was rather similar to the results obtained in the present study after 3 years. Moreover, recent systematic reviews of pharmacotherapy for weight loss including obese patients and obese patients with type 2 diabetes—without an initial VLED—show that the additional weight loss induced by orlistat was from 2.6 to 3.2 kg after 1 year of treatment (13,16,17).

With regard to changes in metabolic risk factors, the orlistat group had a nonsignificant tendency to better out-

comes in relation to glucose-insulin homeostasis than placebo during 3 years, but very similar effects between the two groups were observed concerning changes in lipids and blood pressure (Table 2). Total and LDL cholesterol plus triglycerides were significantly reduced after the VLED-induced major weight loss, but in contrast to several other studies of orlistat (18) there were no additional effects of orlistat on these lipids in the present study. Thus, the effects of orlistat on risk factors seemed to be less pronounced than shown in several other studies (10,18–20). Because we allowed supplementary treatment with antidiabetes medications, statins, and antihypertensive medications, it could be suggested that this comedication may have influenced the result. This possibility cannot completely be excluded, but the number of subjects who were on medication for these risk factors was similar between the two groups during the study. Another explanation could be that the improvement in all risk factors induced after the VLED treatment was so pronounced that the possible specific beneficial effect of orlistat observed in many other studies might be somehow obscured by these initial large weight loss. Finally, compared with several other placebo-controlled studies (21–23), the lifestyle intervention alone plus placebo was markedly effective in the present study.

Although the specific effects of orlistat on risk factors were modest or lacking on some risk factors, orlistat treatment for 3 years was associated with a significant reduction of the development of type 2 diabetes. It was not possible to clarify from the present study whether this is a specific effect of orlistat or whether it is due to the extra 2.2- to 2.4-kg weight loss maintenance induced by orlistat. However, these findings are in accordance with the 4-year XENDOS Study, in which the development of type 2 diabetes was reduced by 37% in the orlistat group compared with the placebo group (14). That orlistat may reduce the development of diabetes and can improve glucose-insulin homeostasis has also been shown by others (13). Other lifestyle interventions with focus on weight loss also have shown reduced development of type 2 diabetes in association with moderate weight loss (24,25).

Our study is one of the few studies of obesity to achieve an approximately equal sex distribution. In the subgroup analysis, the differences in weight loss between orlistat and placebo were more pronounced in women compared with men. The reason for this sex-specific effect might be influenced by the fact that women on placebo were not able to maintain their body weight loss as well as men (only 5.3% weight loss in women versus 7.5% in men). These sex differences should, however, be investigated in more detail in future studies.

The absolute amount of weight loss obtained in the present study is quite pronounced compared with several other pharmacotherapy and lifestyle interventions with maintained weight loss of 9.6 kg after 1.5 years and of 7.3 kg after 3 years in the lifestyle alone plus placebo group and losses of 11.7 kg after 1.5 years and of 9.3 kg after 3 years in the lifestyle plus orlistat group. There may be more reasons for these findings, but the most important may be that in our study design we selected only those participants for randomization who were able to lose at least 5% of their weight during the 8-week VLED, which was ~80% of all who started VLED. Thereby, we have selected the most compliant obese patients for the study, which will result in better weight loss results than if all participants were included. This kind of program might, however, be well suitable for most treatment settings. As a lipase inhibitor, orlistat may theoretically compromise the uptake of fat soluble vitamins. In the XENDOS Study, a significant decrease in the level of fat soluble vitamins was found in the orlistat group after 4 years but the mean level remained within its reference range for all the vitamins during the 4 years (14). These findings, however, indicate that it is rational to give a vitamin supplement together with orlistat.

In conclusion, we found that 3 years of treatment with the lipase inhibitor orlistat modestly reduces weight regain after a major initial VLED-induced weight loss in abdominally obese subjects. Notably, a significant reduction in the development of type 2 diabetes was observed during 3 years of orlistat treatment compared with placebo. Thus, orlistat may be a useful adjunct to conventional dietary and lifestyle treatment of high-risk obese subjects. Lastly, this study indicates that an initial VLED treatment is very efficacious when incorporated into a more general strategy in the treatment of obesity. This approach seems to result in large and rapid weight losses leading to pronounced improvements in the metabolic risk factors.

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